

Successful Use of Intraperitoneal Daptomycin in the Treatment of Vancomycin-Resistant Enterococcus Peritonitis

Sarah C. Huen, MD,¹ Isaac Hall, MD,¹ Jeffrey Topal, MD,² Rex L. Mahnensmith, MD,¹ Ursula C. Brewster, MD,¹ and Ali K. Abu-Alfa, MD¹

Peritoneal dialysis-associated peritonitis from such resistant organisms as vancomycin-resistant enterococci increasingly is occurring and is challenging to treat. We describe 2 cases of vancomycin-resistant enterococcus peritonitis successfully treated with intraperitoneal daptomycin. Both patients were on automated peritoneal dialysis therapy with culture-positive vancomycin-resistant *Enterococcus faecium* peritonitis and were treated with 10 to 14 days of intraperitoneal daptomycin given every 4 hours through manual peritoneal dialysate exchanges. Despite the known degradation in dextrose solutions, intraperitoneal daptomycin was effective in clearing both infections. Neither patient experienced a relapse or repeated peritonitis. Additional studies of dosing and pharmacokinetics of intraperitoneal daptomycin in the treatment of patients with vancomycin-resistant enterococcus peritonitis are needed.

Am J Kidney Dis xx:xxx. © 2009 by the National Kidney Foundation, Inc.

INDEX WORDS: Peritoneal dialysis; vancomycin-resistant enterococcus; peritonitis; daptomycin.

Peritoneal dialysis (PD)-associated peritonitis caused by resistant organisms is increasingly common and is clinically challenging to treat. Successful treatment of patients with vancomycin-resistant enterococcus (VRE) peritonitis with intraperitoneal (IP) daptomycin has not been described. The International Society for Peritoneal Dialysis (ISPD) guidelines do not delineate recommendations for PD catheter removal in patients with such infections.¹ We describe 2 cases of VRE peritonitis associated with PD treated with IP daptomycin resulting in eradication of the infection without removal of the catheter.

CASE REPORTS

Case 1

A 52-year-old African American woman with end-stage renal disease had been on automated PD (APD) therapy for 2 years when she presented from an extended-care facility with hypotension and suspected peritonitis. Two months before, she had been hospitalized with sepsis and treated empirically with intravenous (IV) vancomycin and piperacillin/tazobactam. *Clostridium difficile* infection ultimately was diagnosed and treated with oral vancomycin. Residual creatinine clearance was 0.7 mL/min (0.01 mL/s) 5 months before presentation.

On presentation, the patient was afebrile, blood pressure was 85/54 mm Hg, and heart rate was 100 beats/min. Abdominal examination findings were significant for mild diffuse tenderness. There was no expressible pus, drainage, or erythema surrounding the catheter exit site. The tunnel was not tender. An abdominal film showed a malpositioned catheter with the tip in the left midabdomen. Initial dialysate cell count was 2,200 cells/ μ L (75% granulocytes). IV linezolid and IP daptomycin treatment was initiated because

dialysate cultures sent from the extended-care facility grew vancomycin-resistant *Enterococcus faecium*. The minimal inhibitor concentration (MIC) was not reported for daptomycin. IP daptomycin initially was administered at 100 mg/L for a 6-hour dwell. On treatment day 2, linezolid therapy was discontinued and the IP daptomycin dose was changed to 20 mg/L, with heparin 250 U/L given every 4 hours through manual 2-L PD exchanges using 1.5% dextrose solutions. On day 3 of treatment, 8 mg of alteplase was instilled into the PD catheter and flushed with 10 mL of normal saline. On day 7, cell count normalized to 23 cells/ μ L (Fig 1). All dialysate cultures sent after the initiation of IP daptomycin therapy had negative results. She was treated for 10 days with IP daptomycin. Subsequently, the PD catheter was laparoscopically repositioned without its removal. At 1 and 3 months posttreatment, dialysate culture results were negative and cell counts were normal (<50 cells/ μ L). At the time of writing, the patient remains on APD therapy and is clinically well without signs of peritonitis 9 months after treatment of VRE peritonitis.

Case 2

A 35-year-old African American woman with end-stage renal disease on APD therapy for 3 years presented with 5 days of abdominal pain, nausea, vomiting, and constipation. Her PD history is significant for 3 prior episodes of peritonitis: *Klebsiella pneumoniae* peritonitis 1 year prior, coagulase-

From the Sections of ¹Nephrology and ²Infectious Diseases, Yale School of Medicine, New Haven, CT.

Received October 22, 2008. Accepted in revised form December 14, 2008.

Address correspondence to Ali Abu-Alfa, MD, PO Box 208029, 333 Cedar St, New Haven, CT 06520-8029. E-mail: ali.abu-alfa@yale.edu

© 2009 by the National Kidney Foundation, Inc.

0272-6386/09/xx0x-0001\$36.00/0

doi:10.1053/j.ajkd.2008.12.017

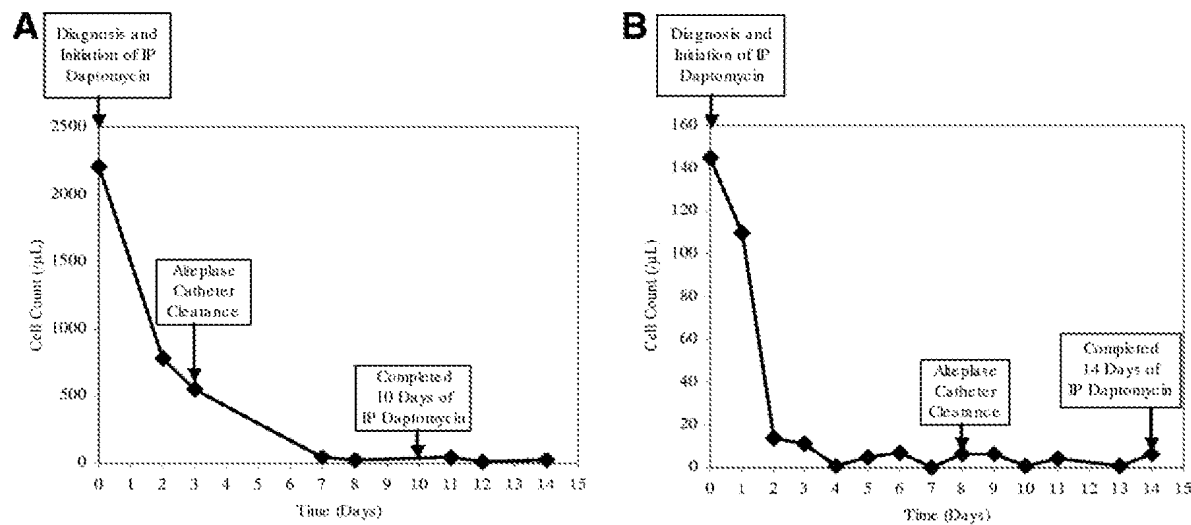


Figure 1. Peritoneal cell count response to intraperitoneal (IP) daptomycin therapy for (A) patient 1 and (B) patient 2.

negative *Staphylococcus* species peritonitis 3 months prior, and culture-negative peritonitis 1 month prior treated empirically with IP vancomycin, ceftazidime, and gentamicin, then oral ciprofloxacin and IP vancomycin as an outpatient. Residual clearance was 1.6 mL/min 3 months before presentation.

The patient initially presented to the PD clinic with a 2-day history of mild abdominal pain and constipation. Dialysate, which was not cloudy, was sent from the clinic for culture. Her bowel regimen was intensified and she was empirically treated for presumed peritonitis with IP vancomycin and gentamicin. Five days later, cultures from the clinic subsequently grew vancomycin-resistant *E. faecium* sensitive to daptomycin (MIC, 4 μg/mL) and gentamicin (MIC, <500 μg/mL). She was admitted to the hospital.

On presentation, the patient was afebrile, blood pressure was 128/90 mm Hg, and heart rate was 81 beats/min. Abdominal examination findings were significant for diffuse tenderness. There was no expressible pus, drainage, or erythema around the PD exit site. Initial dialysate cell count was 145 cells/μL (88% granulocytes). IP daptomycin and gentamicin therapy were initiated at 20 mg/L and 4 mg/L, respectively. Heparin, 500 units/L, was given continuously every 4 hours using 2-L manual exchanges of 1.5% and 2.5% dextrose solutions. On the day of admission, peritoneal cultures again grew vancomycin-resistant *E. faecium*. Dialysate culture results after day 2 of IP daptomycin treatment were negative. By day 3, IP gentamicin therapy was discontinued because cell count (14 cells/μL) and abdominal examination findings had normalized (Fig 1). On day 8 of treatment, 8 mg of alteplase was instilled into the PD catheter and flushed with 10 mL of normal saline. She was treated for a total of 14 days with IP daptomycin, with clearance of peritoneal cultures. The PD catheter was left in place. At the time of writing, the patient remains on APD therapy. The most recent culture results 7 months posttreatment are negative and cell count is normal (22 cells/μL).

DISCUSSION

VRE was described first in the 1980s and has since become increasingly more prevalent, causing infections that include PD-associated peritonitis. Both patients described had multiple risk factors implicated in developing VRE infection, including recent hospitalization, VRE stool carriage, and exposure to broad-spectrum antibiotics, especially vancomycin.²

Treatment of patients with VRE peritonitis poses several challenges, including limited antimicrobial agents available. New agents with activity against VRE recently have been introduced, including linezolid, quinopristin/dalfopristin, and daptomycin. However, data about their efficacy, dosing regimens, and means of administration for patients with VRE peritonitis are lacking. Several case reports of PD-associated VRE peritonitis have been described.³⁻⁸ Antimicrobial agents used in these cases included IV chloramphenicol, IV gentamicin, IV ampicillin, oral and IV linezolid, and IV and IP quinopristin/dalfopristin. One patient in the case series described by Troidle et al⁴ was reported to have cleared VRE peritonitis with IP vancomycin and ceftazidime without catheter change or removal. This is surprising because enterococci are inherently resistant to cephalosporins. The investigators believe the MIC was lower than the vancomycin level achieved. All other surviving patients reported in

Table 1. Summary of Intraperitoneal Daptomycin Use For Peritoneal Dialysis–Associated Vancomycin-Resistant Enterococcus Peritonitis

	Case 1	Case 2	Comments
Dose	100 mg of daptomycin/L of dialysate \times 6 h, then 20 mg of daptomycin/L of dialysate	20 mg of daptomycin/L of dialysate	5 \times the minimal inhibitory concentration of $\leq 4 \mu\text{g/mL}$ reported in the literature for vancomycin-resistant <i>Enterococcus faecium</i> Unclear role for a loading dose of intraperitoneal daptomycin
Dialysate composition	All 1.5% dextrose low calcium (2.5 mEq/L) dialysate	1.5% and 2.5% dextrose, regular calcium (3.5 mEq/L) dialysate	4.25% dextrose dialysate was not used in either patient
Means of administration	Injection of aliquoted daptomycin into dialysate bag immediately before peritoneal infusion Manual 3- to 4-h dwell	Injection of aliquoted daptomycin into dialysate bag immediately before peritoneal infusion Manual 3- to 4-h dwell	Daptomycin is stable in 5% dextrose solutions for only 4 h at room temperature
Length of treatment	10 d	14 d	Optimal length of treatment remains to be determined

the literature required either catheter change or removal.

Daptomycin is a cyclic lipopeptide with rapid concentration-dependent bactericidal activity against almost all gram-positive pathogens.^{9,10} Its extensive protein binding and lack of diffusion into PD fluid suggests that systemically administered daptomycin would not achieve therapeutic concentrations in PD fluid.¹¹ Thus, IP daptomycin is required to treat patients with VRE peritonitis. Although optimal in vivo dosing of IP daptomycin has not been reported, in vitro studies have shown bactericidal pH-independent killing of a number of susceptible organisms grown in 2.5% dextrose dialysate at all concentrations used (10, 30, and 100 mg/L).¹² In our patients, daptomycin dose was calculated as 5 times the MIC of $4 \mu\text{g/mL}$ or less reported in the literature for vancomycin-resistant *E faecium* (Table 1).^{9,13}

An important consideration in prescribing IP daptomycin is that it is unstable in dextrose solutions. Patent information for buffer solutions shows that daptomycin degrades in 5% dextrose solutions at a rate of 15% to 20% at 24 hours at room temperature.¹⁴ According to Cubist Pharmaceuticals Inc (Lexington, MA), the manufacturer of daptomycin, through direct communication, Cubicin (daptomycin) is stable for 4 hours in a 5% dextrose-water solution and for 2.5 hours in 5% dextrose in 0.45% saline at room tempera-

ture. Therefore, in the patients discussed, daptomycin was injected into the dialysate just before peritoneal infusion, and the duration of IP dwells was limited to 4 hours (Table 1). In vitro studies showed a continued bactericidal effect in 2.5% standard dialysate at 37°C up to 24 hours, suggesting that a 4-hour dwell will not significantly affect the action of daptomycin.¹² Further study of the pharmacokinetics of IP daptomycin is required in the various dialysate dextrose concentrations. Neither serum nor dialysate drug concentrations were measured after a 4-hour IP dwell. Although both patients had minimal residual kidney function, need for IP dosage adjustments in patients with greater glomerular filtration rates is unknown. However, the drug is being administered IP every 4 hours and has a significantly prolonged elimination half-life in patients with creatinine clearance less than 30 mL/min ($<0.50 \text{ mL/s}$), which suggests that such decreased glomerular filtration rates are not likely to affect dosage to a significant degree. Despite the known degradation in dextrose solutions, IP daptomycin was effective in clearing VRE peritonitis in the 2 patients described. No adverse effects of IP daptomycin were noted in either patient.

IP daptomycin is effective in treating VRE peritonitis in PD patients. Two patients were successfully treated with a 10- to 14-day course of IP daptomycin with salvage of the catheter. Neither patient experienced a relapse or devel-

oped repeated peritonitis. Further studies are required to determine the best dosing regimen and pharmacokinetics of IP daptomycin, especially in dextrose-containing solutions, but the doses used here appear to be safe and effective. This approach can be attempted in otherwise stable patients who show signs of quick recovery after therapy is initiated. In patients who do not meet these criteria, catheter removal should be considered.

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: None.

REFERENCES

1. Piraino B, Bailie GR, Bernardini J, et al: Peritoneal dialysis-related infections recommendations: 2005 Update. *Perit Dial Int* 25:107-131, 2005
2. Chavers LS, Moser SA, Benjamin WH, et al: Vancomycin-resistant enterococci: 15 Years and counting. *J Hosp Infect* 53:159-171, 2003
3. Carey HB, Troidle L, Kliger AS, Finkelstein FO: Peritonitis due to vancomycin-resistant enterococci: A case report and review of the literature. *Semin Dial* 12:333-336, 1999
4. Troidle L, Kliger AS, Gorban-Brennan N, Fikrig M, Golden M, Finkelstein FO: Nine episodes of CPD-associated peritonitis with vancomycin resistant enterococci. *Kidney Int* 50:1368-1372, 1996
5. Lynn WA, Clutterback E, Want S, et al: Treatment of CAPD-peritonitis due to glycopeptide-resistant *Enterococcus faecium* with quinupristin/dalfopristin. *Lancet* 344:1025-1026, 1994
6. Bailey EM, Faber MD, Nafziger DA: Linezolid for treatment of vancomycin-resistant enterococcal peritonitis. *Am J Kidney Dis* 38:E20, 2001
7. Troidle L, Gorban-Brennan N, Kliger AS, Finkelstein FO: A 5-year experience with vancomycin-resistant enterococcus peritonitis [XIXth Annual Conference on Peritoneal Dialysis Abstract]. *Perit Dial Int* 19:S37, 1999
8. Williams PF: Compassionate use of synergicid in the treatment of VRE peritonitis—A report of 4 cases [XIXth Annual Conference on Peritoneal Dialysis Abstract]. *Perit Dial Int* 19:S38, 1999
9. Schriever CA, Fernandez C, Rodvold KA, Danziger LH: Daptomycin: A novel cyclic lipopeptide antimicrobial. *Am J Health Syst Pharm* 62:1145-1158, 2005
10. Carpenter CF, Chambers HF: Daptomycin: Another novel agent for treating infections due to drug-resistant gram-positive infections. *Clin Infect Dis* 38:994-1000, 2004
11. Salzer W: Antimicrobial-resistant gram-positive bacteria in PD peritonitis and the newer antibiotics used to treat them. *Perit Dial Int* 25:313-319, 2005
12. Hermesen ED, Hovde LB, Hotchkiss JR, Rotschafer JC: Increased killing of staphylococci and streptococci by daptomycin compared with cefazolin and vancomycin in an in vitro peritoneal dialysate model. *Antimicrob Agents Chemother* 47:3764-3767, 2003
13. Clinical and Laboratory Standards Institute (CLSI): Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Information Supplement. Wayne, PA, Clinical and Laboratory Standards Institute; 2007:26(1)
14. Inman EL, Kirsch LE, inventors: LILLY CO ELI (US), assignee. An improved diluent formulation for daptomycin. Patent EP0386951, 1990